**REMARKS**

Revised claims 6-17 and new claims 18-44 remain to be examined in this application. The requisite fee of $826.00 U.S. is enclosed for the new claims 18-44. If any further fees are required they should be taken from Deposit Account Number 08-3255 and advise Applicants' Agent. No new subject matter was added by the amendment made to the claims above.

Applicants propose to deal with the Examiner's grounds for rejection and the objections made by the Examiner in the order set out in the Official Action dated April 16, 1996.

**OATHS OR DECLARATION**

Applicants have reviewed the comments of the Examiner in paragraph 4 of page 2 of the Official Action and herewith enclose documents entitled "Declaration, Power of Attorney and Petition" executed by Drs. Rolf Edgar Falk and Samuel Simon Asculai which refers to the Canadian Patent Application Serial No. 2,061,566 from which Applicants claimed convention priority and the earlier filed United States Patent Application 07/675,908 from which they claimed this application is a Continuation-in-Part Application. Applicants believe that they have correctly completed these documents and the Examiner is respectfully requested to review the following submissions:

> Applicant previously (in their response filed January 13, 1995) incorporated Application 07/675,908 by reference in this application that this application (Application 07/838,675) is a Continuation-in-Part Application of Application 07/675,908 which application

07/675,908 was incorporated herein by reference (as stated in the response filed the 13th day of January, 1995).

The Examiner is thanked for her consideration in this regard.

**LITERATURE CITATIONS**

The Examiner objects to the specification because the reference to Jerne, Moller, Burnett, Lala, Romans and Falk are not accompanied by any citation or a copy of the article. Applicants enclose articles by Lalam, Romans and Falk which are cited on page 10 and 12 of the specification. With respect to articles by Jerne, Burnett and Moller, Applicants will provide upon receipt of same.

**OBJECTION TO CLAIM 13**

With respect to the Examiner's objection in paragraph 6 of page 2 of the Official Action relating to claim 13, line 10, Applicants have amended the pertinent portion of the claim.

**CLAIM REJECTIONS - 35 U.S.C. §112**

The Examiner has objected to the specification under 35 U.S.C. §112, first paragraph on the grounds that the specification does not provide support for the invention as is now claimed.

Applicants respectfully traverse this conclusion. In Application Serial No. 07/675,908 discloses at page 26, lines 32-37 as follows:

"The hyaluronic acid and salts thereof may be utilized at varying doses - 1- to 1000 mg/70 kg person with the optimal doses tending to range between 50 and 350 mg/70 kg individual. As there is no toxicity, the hyaluronic acid can obviously be administered in a dose excess (for example 3000 mg/70 kg individual) without any adverse effects."

The application also discloses the use of the formulations comprising hyaluronan for the treatment of cancer (see page 24, lines 20-24; page 25, line 26 to page 26, line 31; page 26, line 38 to page 27, line 37; page 34, lines 5-10 and 33-38; page 35, lines 31 to page 36, line 8; and Cases I - XXXVII at pages 36-66).

Basal cell carcinoma is a form of cancer. In this application (Application Serial No. 07/838,675), there is taught at least two effects - (1) the successful treatment of basal cell carcinoma by the use of formulations comprising hyaluronic acid and NSAIDS (compounds which inhibit prostaglandin synthesis) in the amounts of between about 1% and about 3% by weight of the form hyaluronic acid and between about 1% and about 5% by weight of the NSAID and (2) the accumulation of the formulation in the epidermis (see page 24-25). Thus this accumulation enables the basal cell carcinoma to be treated. This accumulation is as a result of administration of the formulations. The treatment as shown in the examples is successful because of the application of the formulations. Two specific amounts are specifically disclosed in the application - one of $20mg/cm^2$ of the skin to which the formulation is applied shows accumulation (see page 31) and the other 2g shows there is **no penetration into the blood stream and thus there would appear to be passage into the skin**

**and accumulation of the formulation** containing the hyaluronic acid and NSAID in the skin. This accumulation is shown in the tests at page 28-33 and pages 49-51 of the application. The blood level tests at pages 49-51 of the specification show that the formulation does not enter the blood and thus would be accumulated in the skin and discharged through the lymphatic system. Applicants submit that persons skilled in the art would have no trouble whatsoever in conducting applications on a limited number of individuals having basal cell carcinoma or arrange for applications to be conducted on individuals having basal cell carcinoma using various amounts of the formulations taught in the application to determine optimal dosage amounts. These applications would require a minimum effort and do not constitute undue experimentation in Applicants' respectful submission for the administration of the formulations to resolve and treat the basal cell carcinoma. The 2g of the formulation is an amount Applicant understands which would be a glob on the finger of an individual. This glob would be rubbed into the skin. Persons skilled in the art would in Applicants' respectful submission, knowing these formulations work, probably include the two specific amounts in their applications to determine the optimal dosage amounts. Such persons skilled in the art know that the formulations work. Patients could be told to apply these formulations in large amounts and rule them in knowing the formulations work.

In this regard, the Examiner's attention is directed to United States Court of Appeal's Decision dealing with "Sufficiency of Disclosure" under 35 U.S.C. §112, *In Re Norman K. Alton*, 37 U.S.P.Q. 2d, 1578. In that case, the United States Court of Appeal's stated as follows:

"The issue of whether a patent specification adequately describes the subject matter claimed is a **question of fact**. Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). We review questions of fact arising from Board rejections under a clearly erroneous standard. In re Caveney, 761 F.2d 671, 674, 225 USPQ 1, 3 (Fed. Cir. 1985). We review questions of law de novo. Electronic Design & Sales, Inc., v. Electronic Data Systems Corp., 954 F.2d 713, 715, 21 USPQ2d 1388, 1390 (Fed. Cir. 1992).

The adequate written description requirement, which is distinct from the enablement and best mode requirements,[3] serves 'to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him; how the specification accomplishes this is not material.' In re Wertheim, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). In order to meet the adequate written description requirement, the applicant does not have to utilize any particular form of disclosure to describe the subject matter claimed, but 'the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.' In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (citation omitted). Put another way, 'the applicant must ... convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention.' Vas-Cath, 935 F.2d at 1563-64, 19 USPQ2d at 1117. Finally, we have stated that '[p]recisely how close the original description must come to comply with the description requirement of section 112 must be determined on a case-by-case basis.' Eiselstein v. Frank, 52 F.3d 1035, 1039, 34 USPQ2d 1467, 1470 (Fed. Cir. 1995) (quoting Vas-Cath, 935 F.2d at 1561, 19 USPQ2d at 1116).

"It is well settled that the question of whether a specification provides an adequate written description of the subject matter of the claims is an issue of fact. Therefore, the examiner was in error when he stated that the Wall declaration, which attempted to shed light on whether the '451 specification adequately described the subject matter of claim 70, addressed a legal issue.

Additionally, the examiner interpreted the Wall declaration as offering opinion evidence, rather than factual evidence, on the adequate written description issue. The Wall declaration's assertion that '[m]odifying the residue at position 81 would have no effect on [disulfide bridge formation] because neither [asparagine] nor lysine can participate in disulfide bridge formation' is a factual statement, however. So too is the statement that changing the amino acid at position 81 would involve a modification in subunit IF-2, 'requiring an entirely separate series of manipulations of the complete [amino acid] sequence to generate this different class of analog.' We do not read the declaration as asserting an opinion on the patentability of the claimed IFN- analog. Rather, the declaration is offering factual evidence in an attempt to explain why one of ordinary skill in the art would have understood the specification to describe the modification involving the deletion of the first three amino acids independently of the modification at position 81. Dr. Wall's use of the words "it is my opinion" to preface what someone of ordinary skill in the art would have known does not transform the factual statements contained in the declaration into opinion testimony.

The examiner (or the Board, if the Board is the first body to raise a particular ground for rejection) 'bears the initial burden ... of presenting a prima facie case of unpatentability.' In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Insofar as the written description requirement is concerned,

that burden is discharged by 'presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims.' Wertheim, 541 F.2d at 263, 191 USPQ at 97. Thus, the burden placed on the examiner varies, depending upon what the applicant claims. If the applicant claims embodiments of the invention that are completely outside the scope of the specification, then the examiner or Board need only establish this fact to make out a prima facie case. Id. at 263-64, 191 USPQ at 97. If, on the other hand, the specification contains a description of the claimed invention, albeit not in ipsis verbis (in the identical words), then the examiner or Board, in order to meet the burden of proof, must provide reasons why one of ordinary skill in the art would not consider the description sufficient. Id. at 264, 191 USPQ at 98. Once the examiner or Board carries the burden of making out a prima facie case of unpatentability, 'the burden of coming forward with evidence or argument shifts to the applicant.' Oetiker, 977 F.2d at 1445, 24 USPQ2d at 1444. To overcome a prima facie case, an applicant must show that the invention as claimed is adequately described to one skilled in the art. 'After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument.' Id. at 1445, 24 USPQ2d at 1444.

As the Examiner is aware, Applicant has, in subsequent applications, set out lower amounts for application of the formulations containing $5mg/cm^2$ of the form of hyaluronic acid for treating the disease or condition (such as basal cell carcinoma) or higher amounts of $10mg/cm^2$ of the form of hyaluronic acid when treating pain. Applicants have conducted tests where the amounts are less than $5mg/cm^2$. The results, of course, are better where more is applied to the skin (see the enclosed Declaration of Dr. Asculai, paragraphs 3 and 4).

Applicants submit that persons reading this application (07/838,675), even without reference to the previous application (07/675,908) from which this application is a Continuation-in-Part, will note that the amounts indicated at page 31 and page 50-52 of this application (07/838,675) are amounts used for accumulation and which do not go into the blood. Persons skilled in the art reading the application would also know that the formulation works with the concentrations given. Consequently, persons skilled in the art would have very little difficulty testing the formulations for use for successfully treating and resolving basal cell carcinoma (see the enclosed Declaration of Dr. DeVeber). The persons skilled in the art are given the formulations, the percentage concentrations of HA and NSAID and all that need be done by the practitioners is that patients, for example 30 patients, need apply amounts of the formulations for say "30 days" or more with each patient receiving a differing amount from the other patients per application. The choice will be as persons skilled in the art may reasonably choose from this application, such as 20mg/$cm^2$ of the form of hyaluronic acid or 2g of the formulation or other amounts. Such person would know that patients receiving the formulation would just extract some from a container and rub it in. They would instruct the patient that if they wish they could rub in more into each site of basal cell carcinoma. (Remember, persons skilled in the art would also know that there would not be an unlimited amount which the skin could absorb because the skin would have a saturation point of anything applied to it as to what it could take in). These amounts would be determined very readily without undue experimentation by persons skilled in the art. Applicants once again submit that the dosage amount which is referred to in the application at page 51 with respect to non-passage into the blood showing there is an accumulation will lead persons skilled in the art to try this

dosage referred to in this application because the persons skilled in the art know the treatment works. In this regard, the Examiner's attention is directed to the Declaration of George DeVeber, specifically to paragraphs 6 and 7.

In view of the above, it is clear that without undue experimentation, persons skilled in the art would have no difficulty using the formulations in this patent application for the treatment of basal cell carcinoma. Representative claims for the treatment of basal cell carcinoma are now enclosed including the maintenance of the original claim reciting at least 30mg to 60mg of the form of hyaluronic acid in claim 6. Claim 31, a newly added claim, refers to the amount of hyaluronic acid being between 10mg and 1000mg of the form of hyaluronic acid and Claim 13 deals with the dosage amount claimed as an effective amount based on the concentrations of the form of hyaluronic acid and NSAID only. Another new claim (Claim 18) is the combination of dosage amounts of at least 30-60mg of the form of hyaluronic acid and concentrations of hyaluronic acid and NSAID. Applicants submit that these claims are supported by the disclosure. Persons skilled in the art would advise patients to take an effective dosage amounts which are easily determined by minimal tests and applied until the basal cell carcinoma is resolved having regard to the fact that the formulations containing specific concentrations of each of the NSAID and hyaluronic acid are known to work.

Applicants respectfully submit that the claims as amended and the additional new claims are each addressed to persons skilled in the art who would have been taught exemplary formulations from which the dosage amounts can be taken and the dosage amounts are exemplified in the claims. Therefore, Applicants respectfully submit that the Examiner should withdraw the rejection

under 35 U.S.C. §112 which are set forth on pages 3, 4 and 5 of the Office Action mailed April 16, 1996.

In support of this application, Applicant encloses a number of declarations by experts which are filed with application 07/675,908 and additional declarations which relate to this application (07/838,675).

With respect to the Declarations filed with Application 07/675,908, Applicants' agent discussed the Examiner's conclusions (with respect to Application Serial No. 07/675,908) with the foremost authorities of hyaluronic acid in the world today. These "experts" were given a copy of PCT Application PCT/CA90/00306, published under International Publication No. WO 91/04058, which application entered the national phase in the United States under Application Serial No. 07/675,908, together with prior art cited by the Examiner in the prosecution of Application Serial No. 07/675,908 from which this application is a Continuation-in-Part for the separate and additional invention claimed herein (this application also incorporates by reference the earlier teaching of Application Serial No. 07/675,908). These experts were asked what persons skilled in the art would understand from the equivalent of Application Serial No. 07/675,908 and the prior art. These experts, who know what would be understood by persons skilled in the art reading the PCT application and the prior art, as well as the state of the art at the time of the invention, have expressly disagreed with the conclusion reached by the Examiner of Application Serial No. 07/675,908 with respect to the understanding of a person skilled in the art reading Applicants' application and the prior art. In each expert's opinion, Applicants' disclosure of Application Serial No. 07/675,908 is addressed to persons skilled in the art and such person can practice it without undue

experimentation. These conclusions are equally applicable to Applicant's present Application Serial No. 07/838,675 for the additional inventive aspect of dosage amounts and successful treatment of basal cell carcinoma enumerated using formulations containing a percentage of active medicine and a percentage of a form of hyaluronic acid claimed in the claims presented herein.

Each one of the experts was surprised that the invention in Application Serial No. 07/675,908 of Drs. Falk and Asculai worked. Each expert previously thought hyaluronic acid to be inert and, if combined with medicine, would be passive - no different than the prior art cited by the Examiner of Serial No. 07/675,908. Applicants, therefore, enclose with this response, the Declaration of:

1. Professor Torvard Laurent;
2. Dr. Robert Fraser;
3. Professor Ian Constable;
4. Dr. Eva Turley;
5. Dr. Stefan Gustafson;
6. Dr. Adrian Moore;

who are, Applicants respectfully submit and the Examiner will conclude after reading their declarations and curriculum vitae, experts with respect to hyaluronic acid and its use. Their curriculum vitae setting out their qualifications (education, experience and publications) would leave no doubts.

Applicants also enclose with this response the Declaration of Dr. Sanford Roth, who is an expert in pharmakotherapeutics, especially in the areas of analgesia, inflammation and immunomodulation. The Examiner will note

from reading his curriculum vitae that his expertise includes non-steroidal anti-inflammatory drugs (NSAIDS). His qualifications are impeccable. He also refers to two PCT Applications at paragraphs 24-26 which are applications filed subsequent to this application but teach the same formulations (including percentages) but set out minimal dosage amounts ($5mg/cm^2$) for the treatment of disease and condition and 10 $mg/cm^2$ for the treatment of pain. The formulations and some of the examples are identical. He thereafter discusses the prior art.

The other Declaration enclosed which was filed with Application Serial No. 07/675,908 is the Declaration of Stellan Lind. Stellan Lind, while not a technical expert, was involved in the industry relating to hyaluronic acid as a business person and knew the products being experimented with and marketed that contained hyaluronic acid prior to the invention by Drs. Falk and Asculai. He discusses what was known and at what period of time with respect to Application Serial No. 07/675,908. The evidence submitted with this response, in Applicant's respectful submission, even though related to Application Serial No. 07/675,908 is equally applicable to this application (because the declarations specifically describe, according to the experts, what would be understood by persons skilled in the art from the prior art references). This evidence is overwhelming. There is no teaching in Della Valle or any of the references of the prior art or in any continuation of them of the teachings herein.

The additional Declarations enclosed with this response relate to this application (07/838,675) and contain:

1. the additional data presented herein (that found in Dr. Asculai's declaration);
2. the declaration of Dr. George DeVeber, a doctor who would, reading this application, know what dosages to administer and how to determine the suitable dosage.

The Examiner will note that the persons skilled in the art, having learned from this application that the combination of NSAIDS and hyaluronic acid is effective to treat basal cell carcinoma using Applicants' formulations, that such persons could easily design other formulations which would be effective now that it has been found that the use of hyaluronic acid and a drug which inhibits prostaglandin synthesis is effective for the treatment and resolution of basal cell carcinoma.

The Examiner has also objected to the phrases "a number of times daily" and "over a prolonged period of time" and "molecular weight". From the enclosed declaration of Dr. DeVeber, now filed in this case, and Declarations filed in the previous application 07/675,908 (see for example paragraphs 22-28 of Dr. Fraser's Declaration and paragraph 8 of Dr. Moore's Declaration with respect to the expression "molecular weight"), the Examiner will appreciate that persons skilled in the art would know what molecular weights, what period of time to use the formulation and the number of times daily. In fact, persons skilled in the art would use or require the patients to use the formulation for a prolonged period until such time as the treatment successfully resolves the basal cell carcinoma.

In order to overcome the Examiner's objection in paragraph 2 at page 6 of the Office Action and to be consistent with the above statement, Applicants have amended claims 6 and 13 in order to point out and distinctly claim the subject matter which Applicants regard as the invention. Thus, the rejection of the Examiner set forth in paragraphs 1 and 2 on page 6 of the Official Action, mailed April 16, 1996, has been overcome by the submissions advanced and amendments made to the claims.

With respect to paragraph 3 of page 6 of the Office Action, Applicants have amended claim 13 to overcome the Examiner's objection.

With respect to the Examiner's objection to claim 8 and 12, Applicants submit that the claims are neither vague nor indefinite as to the method by which the molecular weight is determined. Applicants' application teaches suitable molecular weight prepared from forms of hyaluronic acid having a molecular weight average of from 150,000 daltons to 750,000 daltons to achieve the claimed effect. This effect is part of a dynamic process of delivery as taught in the application. If the preferred molecular weights of hyaluronic acid are too high, they may be autoclaved to reduce their size. The reason, therefore, is to permit transportation as discussed in the Parent Application Serial No. 07/675,908 and in this application as previously discussed which transports the NSAID to the epidermis to do its job. In other words, the invention is based on the treatment of diseases and conditions (eg. pain, basal cell carcinoma) by the formulations herein wherein hyaluronic acid acts as a transporting agent. Therefore, Applicants respectfully submit that claims 8 and 12, as amended, are clearly supported by the disclosure and persons skilled in the art would have no

difficulty in determine suitable molecular weight of hyaluronic acid which can be used in the formulation. The Examiner's reconsideration is requested.

With respect to the Examiner's objection found in paragraph 2 of page 7 of the Office Action, Applicants have amended the claims in order to overcome the Examiner's objection. In regard to the Examiner's concern with respect to the drug names, Applicant's have amended the claim to refer to these drugs using all lowercase letters.

Applicants note that the Examiner has withdrawn the previous rejections under 35 U.S.C. §103 and the Applicants conclude that, what they have been saying all along, the invention as claimed is new and inventive over the prior art cited by the previous Examiner and those arts provided by the Applicant.

With respect to paragraph 3 of page 6 of the Office Action relating to double patenting, Applicants submit that with the amendments made to this application and that have been made to the claims of Application Serial No. 07/675,908, 08/018,508 and 08/018/754, Applicants submit that the claims claimed herein are patentably distinct over and above Application Serial No. 07/675,908. If the double patenting issue, when claims are allowed with respect to Application Serial No. 08/018,508 and 08/018,754, is of concern to Examiner Fonda, Applicants will file an appropriate Terminal Disclaimer as required (depending on the nature of the claims allowed).

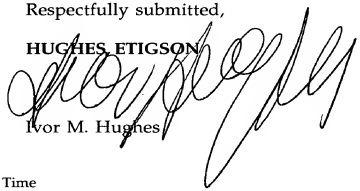
In view of the above submissions, Applicants respectfully submit that the claims in the application are now allowable.

The Examiner will appreciate the extent of the effort Applicants have made in bringing sufficient evidence to the Examiner's attention to enable the Examiner to consider the claims further. Once the Examiner has time to review the materials enclosed with this response, Applicants' agent will contact the Examiner to arrange an appointment to meet with the Examiner to discuss the application.

If the Examiner, in the interim, has any questions, she is respectfully requested to contact Ivor Hughes at (905) 771-6414 collect at her convenience.

Respectfully submitted,

**HUGHES ETIGSON**



Ivor M. Hughes

IMH/STT*kdk

***Enclosures***

1. Requisition for 3 Month Extension of Time
2. Petition pursuant to §1.129(a) to Withdraw Final Rejection
3. Declaration, Power of Attorney and Petition executed by Drs. Rolf Edgar Falk and Samuel Simon Asculai
4. Articles by Lala, Romans and Falk
5. Declaration of Dr. George DeVeber
6. Declaration of Dr. Samuel S. Asculai
7. Declaration of Professor Torvard Laurent;
8. Declaration of Dr. Robert Fraser;
9. Declaration of Professor Ian Constable;
10. Declaration of Dr. Eva Turley;
11. Declaration of Dr. Stefan Gustafson;
12. Declaration of Dr. Adrian Moore;
13. Declaration of Dr. Sanford Roth
14. Declaration of Stellan Lind